your entrance to the knowledge resources of the National Library of Medicine

New Search

Overview
What's New
Help
FAQ

Other NLM Resources
Ordering Info.
Clinical Alerts
ClinicalTrials.gov
HSTAT
LOCATORplus
MEDLINEplus
PubMed
TOXNET

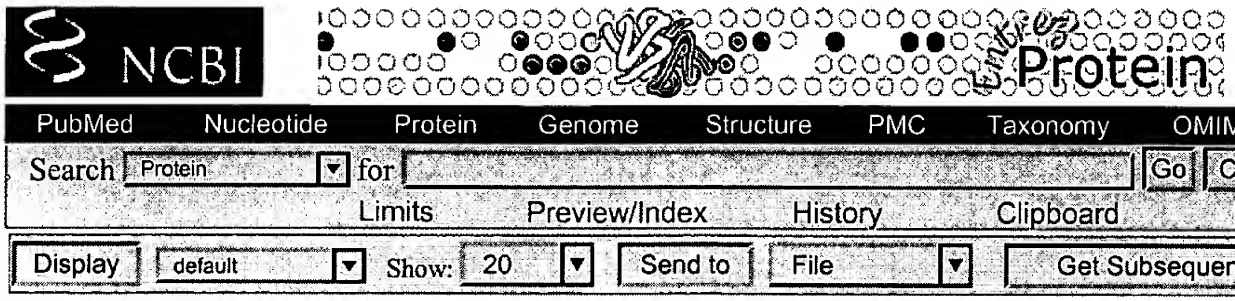
MeSH Term Information

Concept	syntenin
Registry Number	0
Frequency	5
Source	Proc Natl Acad Sci U S A 1997 Dec 9;94(25):13683-8
Entry Date	19980112
Last Revision Date	20000523
Concept Id	C0669068
Heading Mapped To	*Carrier Proteins
Name of Substance	syntenin
Note	PDZ domain-containing protein that binds syndecan proteins; amino acid sequence in first source; GenBank AF000652
Unique ID	C109621

O00560

BLink, Domains, Links

Syntenin 1 (Syndecan binding protein 1) (Melanoma differentiation associated protein-9) (Mda-9) (Scaffold protein Pbp1) (Pro-TGF-alpha cytoplasmic domain-interacting protein 18) (TACIP18)
gi|20455281|sp|O00560|SDB1_HUMAN[20455281]



☐ 1: O00560. Syntenin 1 (Synde...[gi:20455281] BLink, Domains, Links

```
LOCUS       O00560                  298 aa            linear   PRI 15-JUN-2002
DEFINITION  Syntenin 1 (Syndecan binding protein 1) (Melanoma differentiation
            associated protein-9) (Mda-9) (Scaffold protein Pbp1)
            (Pro-TGF-alpha cytoplasmic domain-interacting protein 18)
            (TACIP18).
ACCESSION   O00560
VERSION     O00560  GI:20455281
DBSOURCE    swissprot: locus SDB1_HUMAN, accession O00560;
            class: standard.
            extra accessions:O00173,O43391,created: Jun 15, 2002.
            sequence updated: Jun 15, 2002.
            annotation updated: Jun 15, 2002.
            xrefs: gi: 2198854, gi: 2198855, gi: 2795862, gi: 2795863, gi:
            1916849, gi: 1916850
            xrefs (non-sequence databases): HSSPP31016, MIM 602217,
            InterProIPR001478, PfamPF00595, SMARTSM00228, PROSITEPS50106
KEYWORDS    Cytoskeleton; Membrane; Endoplasmic reticulum; Nuclear protein;
            Phosphorylation; Repeat; Polymorphism.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 298)
  AUTHORS   Lin,J.J., Jiang,H. and Fisher,P.B.
  TITLE     Characterization of a novel melanoma differentiation associated
            gene, mda-9, that is down-regulated during terminal cell
            differentiation
  JOURNAL   Mol. Cell. Differ. 4, 317-333 (1996)
  REMARK    SEQUENCE FROM N.A.
REFERENCE   2  (residues 1 to 298)
  AUTHORS   Grootjans,J.J., Zimmermann,P., Reekmans,G., Smets,A., Degeest,G.,
            Durr,J. and David,G.
  TITLE     Syntenin, a PDZ protein that binds syndecan cytoplasmic domains
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 94 (25), 13683-13688 (1997)
  MEDLINE   98054294
   PUBMED   9391086
  REMARK    SEQUENCE FROM N.A., INTERACTION WITH SYNDECAN-2, AND VARIANT
            SER-69.
REFERENCE   3  (residues 1 to 298)
  AUTHORS   Burbelo,P.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (~JAN-1997)
  REMARK    SEQUENCE FROM N.A.
REFERENCE   4  (residues 1 to 298)
  AUTHORS   Torres,R., Firestein,B.L., Dong,H., Staudinger,J., Olson,E.N.,
            Huganir,R.L., Bredt,D.S., Gale,N.W. and Yancopoulos,G.D.
  TITLE     PDZ proteins bind, cluster, and synaptically colocalize with Eph
            receptors and their ephrin ligands
  JOURNAL   Neuron 21 (6), 1453-1463 (1998)
  MEDLINE   99098206
   PUBMED   9883737
```

WEST

Generate Collection Print

L15: Entry 3 of 10 File: USPT Apr 18, 2000

DOCUMENT-IDENTIFIER: US 6051376 A
TITLE: Uses of mda-6

Detailed Description Paragraph Right (241):
Recent studies by Welch et al. (42) indicate that insertion of a normal chromosome 6 (by the microcell chromosome replacement technique) into the C8161 human melanoma cell line results in a suppression of metastatic, but not tumorigenic potential in nude mice. Treatment of C8161 cells for 4 or 7 days with IFN-.beta.+MEZ (1000 units/ml+10 ng/ml) results in terminal cell differentiation. In contrast, under similar conditions, C8161 cells containing chromosome 6 (Clone 6.1, 6.2 and 6.3) display morphological changes and growth suppression but cells retain proliferative potential, i.e., the combination of agents induces a reversible commitment to differentiation as opposed to terminal differentiation. A lack of terminal differentiation in 6.1, 6.2 and 6.3 cells was demonstrated by removing the test agents and growth in inducer free medium (data not shown). Analysis of gene expression in parental C8161 and 6.1, 6.2 and 6.3 cells indicated differences that correlated with the presence of a normal chromosome 6. Specific differences in gene expression after 4 days incubation with IFN-.beta. and MEZ, alone and in combination, include: (a) induction of IL-8 mRNA (which was identified as an mda cDNA in HO-1 cells treated with IFN-.beta.+MEZ) in MEZ and IFN-.beta.+MEZ treated C8161 cells, but not in 6.1, 6.2 or 6.3 cells; (b) induction of HLA Class I antigen mRNA by IFN-.beta., MEZ and IFN-.beta.+MEZ in C8161, but only by IFN-.beta. and IFN-.beta.+MEZ in 6.1, 6.2 and 6.3 cells; and (c) reduced induction of ISG-15 expression in C8161 cells versus 6.1, 6.2 and 6.3 cells treated with IFN-.beta. and IFN-.beta.+MEZ. The studies briefly described above indicate that IFN-.beta.+MEZ is more effective in inducing terminal differentiation in the less differentiated metastatic C8161 melanoma cells than the more differentiated 6.1, 6.2 and 6.3 cells. This model system should prove useful in determining the role of specific mda genes in expression of the tumorigenic and metastatic phenotype by human melanoma cells.

Detailed Description Paragraph Right (426):
The combination of recombinant human fibroblast interferon (IFN-.beta.) and the antileukemic compound mezerein (MEZ) induces terminal differentiation with an irreversible loss of proliferative capacity in human melanoma cells. Using subtraction hybridization, cDNAs were identified that display enhanced expression in terminally differentiated and growth arrested human melanoma cells (Jiang and Fisher, 1993; Jiang et al., 1994). A specific melanoma differentiation-associated (mda) cDNA, mda-6, is described whose expression inversely correlates with melanoma progression and growth. mda-6 is identical to WAF1/CIP1/SDI1 that encodes the M.sub.r 21,000 protein (p21) that is an inhibitor of cyclin-dependent kinases. Actively growing normal melanocyte, SV40-immortalized human melanocyte and dysplastic nevus cell lines synthesize elevated levels of mda-6 mRNA; whereas, actively proliferating radial and early vertical growth phase primary melanomas as well as metastatic human melanoma cells produce reduced levels of mda-6 mRNA. Treatment of primary and metastatic human melanoma cells with IFN-.beta.+MEZ results in growth inhibition and an increase in mda-6 expression. mda-6 expression also increases when human melanoma cells are grown to high saturation densities or when grown in serum-free medium. Using anti-p53 and anti-p21 antibodies, an inverse correlation is found between p53 and p21 protein levels during growth arrest and differentiation. Induction of growth arrest and terminal differentiation in HO-1 human melanoma cells by IFN-+MEZ results in a temporal decrease in wild-type p53 protein levels with a corresponding increase in p21 levels. In the Matrigel-assisted melanoma progression model, mda-6 expression decreases in early vertical growth phase primary human melanoma cells selected for autonomous or enhanced tumor formation in nude mice. In metastatic human melanoma cells displaying a loss of metastatic potential resulting following introduction of a normal human chromosome 6, mda-6 mRNA levels increase. Taken together, these studies indicate that mda-6 (p21) may function as a

negative regulator of melanoma growth, progression and metastasis.

WEST

Generate Collection Print

L15: Entry 3 of 10 File: USPT Apr 18, 2000

US-PAT-NO: 6051376
DOCUMENT-IDENTIFIER: US 6051376 A

TITLE: Uses of mda-6

DATE-ISSUED: April 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fisher; Paul B.	Scarsdale	NY		
Jiang; Hongping	New York	NY		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Trustees of Columbia University in the City of New York	New York	NY			02

APPL-NO: 8/ 316537 [PALM]
DATE FILED: September 30, 1994

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/143,576 filed Oct. 27, 1993 now U.S. Pat. No. 5,643,761, the contents of which are hereby incorporated by reference.

INT-CL: [7] C12 Q 1/68

US-CL-ISSUED: 435/6; 436/501, 435/69.1, 514/2, 514/44
US-CL-CURRENT: 435/6; 435/69.1, 436/501, 514/2, 514/44

FIELD-OF-SEARCH: 435/6, 435/810, 435/69.1, 436/501, 436/63, 536/22.1, 536/23.1, 536/24.1, 536/24.3-24.33, 514/2, 514/44, 935/77, 935/78

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5302706	April 1994	Smith	536/23.2
☐	5643761	July 1997	Fisher et al.	435/91.1

OTHER PUBLICATIONS

Singh et al. (1993) Carcinogenesis, vol. 14, No. 4, pp. 699-704.
Sumiya et al. (1990) European Journal of Cancer, vol. 26, No. 7, pp. 786-789.
Jiang et al. (1994) Molecular and Cellular Differentiation, vol. 2, No. 3, pp. 221-239.

Hara, E., et al. (1993) Anal. Biochem., 214:58-64 (Exhibit B).
Rubenstein, J.L.R., et al. (1990) Nucleic Acids Research, 18:4833-42 (Exhibit C).
Hara, E., et al. (1991) Nucleic Acids Research, (25) : 7097-7104 (Exhibit D).
Maniatis, T., et al. (1982) Molecular Cloning: A Laboratory Manual, pp. 224-228 (Exhibit E).
Travis, G., et al. (Mar. 1988) Proc. Natl. Acad. Sci., USA, 85:1696-1700 (Exhibit F).
Duguid, J.R., et al. (Aug. 1988) Proc. Natl. Acad. Sci. USA, 85:5738-5742 (Exhibit G).
Herfort, M.R. and Garber, A.T. (Nov. 1991) BioTechniques, 11 (5): 598-603 (Exhibit H).
Lee, S.W., et al. (Apr. 1991) Proc. Natl. Acad. Sci., USA, 88:2825-2829 (Exhibit I).
Sive, H.L., et al. (Nov. 1988) Nucleic Acids Research, 16 (22):10937 (Exhibit J).
Wieland, I., et al. (Apr. 1990) Proc. Natl. Acad. Sci., USA, 87:2720-2724 (Exhibit K).

ART-UNIT: 165
PRIMARY-EXAMINER: Marschel; Ardin H.
ATTY-AGENT-FIRM: White; John P. Cooper & Dunham LLP

ABSTRACT:

This invention provides a method of generating a subtracted cDNA library of a cell comprising: a) generating a cDNA library of the cell; b) isolating double-stranded DNAs from the cDNA library; c) releasing the double-stranded cDNA inserts from the double-stranded DNAs; d) denaturing the isolated double-stranded cDNA inserts; e) hybridizing the denatured double-stranded cDNA inserts with a labelled single-stranded nucleic acid molecules which are to be subtracted from the cDNA library; and f) separating the hybridized labeled single-stranded nucleic acid molecule from the double-stranded cDNA inserts, thereby generating a subtracted cDNA library of a cell. This invention also provides different uses of the subtracted library.

8 Claims, 63 Drawing figures

WEST

Generate Collection Print

L15: Entry 4 of 10 File: USPT May 11, 1999

DOCUMENT-IDENTIFIER: US 5902576 A
TITLE: Antitumor pharmaceutical composition comprising IL-6 transfected cells

Brief Summary Paragraph Right (3):
Experiments in vitro showed that the growth of human breast carcinoma lines MCF-7, SK-BR3, T47D and ZR-75.1 was inhibited by human recombinant IL-6 (rIL-6). In murine and human myeloid leukemia lines, human rIL-6 induced terminal differentiation and growth arrest and in fresh leukemic cells isolated from acute myeloid leukemia (AML) patients, treatment with human rIL-6 increased the proportion of cells with a differentiated phenotype. In vivo experiments using FBL-3 erythroleukemia showed that administration of high does human rIL-6 induced a strong anti-tumor CTL activity that cured the tumor-bearing mice. Experiments with several moderately immunogenic, metastatic murine sarcoma lines (MCA 105,106,203) and a colon carcinoma line MC-38 showed that systemic administration of human rIL-6 reduced substantially the number of metastatic lesions.

WEST

Generate Collection Print

L15: Entry 4 of 10 File: USPT May 11, 1999

US-PAT-NO: 5902576
DOCUMENT-IDENTIFIER: US 5902576 A

TITLE: Antitumor pharmaceutical composition comprising IL-6 transfected cells

DATE-ISSUED: May 11, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Eisenbach; Lea	Rehovot			ILX
Porgador; Angel	Rishon Lezion			ILX
Feldman; Michael	Rehovot			ILX
Revel; Michel	Rehovot			ILX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
YEDA Research and Development Co. Ltd. at Weizmann Institute of Science	Rehovot			ILX	03

APPL-NO: 8/ 430248 [PALM]
DATE FILED: April 28, 1995

PARENT-CASE:
This is a continuation of application Ser. No. 07/964,719 filed on Oct. 22, 1992 now abandoned.

INT-CL: [6] A61 K 48/00, C12 N 5/00

US-CL-ISSUED: 424/93.21; 514/44, 435/325, 435/366
US-CL-CURRENT: 424/93.21; 435/325, 435/366, 514/44

FIELD-OF-SEARCH: 514/44, 424/93.21, 435/240.1, 435/325, 435/366

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5188828	February 1993	Goldberg et al.	514/8

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0220574	October 1986	EPX	
0326120	January 1989	EPX	
3922444A1	October 1991	DEX	
9205262	April 1992	WOX	
WO92 05262	April 1992	WOX	
WO93 06867	April 1993	WOX	

OTHER PUBLICATIONS

Vieweg et al (1995) Cancer Investigation 13, 193-201.
Zilberstein et al., The EMBO Journal, vol. 5, No. 10, pp. 2529-2537 (1986).
Black et al, Endocrinology, vol. 128 No. 5, pp. 2657-2659 (May 1991).
Mullen et al, Cancer Res, vol. 52, pp. 6020-6024 (Nov. 1, 1992).
Scala et al, J. Exp. Med. vol. 172 pp. 61-62 (Jul. 1990).
Mule et al., J. Exp. Med., vol. 171 pp. 629-636 (Mar. 1990).
Porgador et al., "Interleukin 6 gene transfection into Lewis lung carcinoma umor cells suppresses the malignant phenotype . . ." Cancer Research, 52:3679-3686 (1992).
Russell, SJ. "Lymphokine gene therapy for cancer" Immunotherapy Today, vol. 11, No. 6, pp. 196-200 (1990).
Revel, M., Experientia 45:549-55 (1989).
Kishimoto, T., Blood 74:1-10 (1989).
Sehgal, P., Proc. Soc. Exp. Biol. Med. 195:183-191 (1990).
Eisenbach, L., et al., Int. J. Cancer 34:567-573 (1984).
Plaksin, D., et al., Proc. Natl. Acad. Sci. USA 85:4463-4467 (1988).
Southern, P., et al., J. Mol. Appl. Genet. 1:327-341 (1982).
Watanabe, Y., et al., Proc. Natl. Acad. Sci. USA 86:9456-9460 (1989).
Gansbacher, B., et al., Cancer Res. 50:7820-7825 (1990).
Fearon, E., et al., Cell. 60:397-403 (1990).
Ley, V., et al., Eur. J. Immunol. 21:851-854 (1991).
Gansbacher, B., et al., J. Exp. Med. 172:1217-1224 (1990).
Tepper, R., et al., Cell. 57:503-512 (1989).
Chirgwin, J. et al., Biochemistry 18:5294-5298 (1979).
Ozato, K. et al., J. Immunol. 126:317-321 (1981).
Eldar H., et al., J. Biological Chemistry. 265:13290-13296 (1990).
Gilboa, E., et al., BioTechniques. 4:504-512 (1986).
Markowitz, D., et al., J. Virology 62:1120-1124 (1988).
Markowitz, D., et al., J. Virology 167:400-406 (1988).

ART-UNIT: 162
PRIMARY-EXAMINER: Crouch; Deborah
ATTY-AGENT-FIRM: Kohn & Associates

ABSTRACT:

An anti-tumor pharmaceutical composition includes cells into which a gene encoding human IL-6 has been inserted. A method of treatment of a patient suffering from cancer to prevent and/or inhibit the development of metastases by administering to the patient the anti-tumor pharmaceutical composition including the above mentioned cells.

14 Claims, 9 Drawing figures

L14 ANSWER 31 OF 36 MEDLINE

ACCESSION NUMBER: 97468059 MEDLINE
DOCUMENT NUMBER: 97468059 PubMed ID: 9327203
TITLE: Regulation of ion **transport** by protein-protein interaction domains.
AUTHOR: Staub O; Rotin D
CORPORATE SOURCE: Hospital for Sick Children, Division of Respiratory Research, Toronto, Ontario, Canada.
SOURCE: CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, **(1997 Sep)** 6 (5) 447-54. Ref: 47
Journal code: B4H; 9303753. ISSN: 1062-4821.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971103

AB Protein-protein interaction via specific modular domains has been implicated in the regulation of many signalling pathways. Recently, such modules, in particular WW, Src homology-3 and **PDZ** domains, have been shown to regulate localization, clustering and function of several ion channels and **transporters**, including the epithelial Na+ channel, K+ channel and ionotropic neurotransmitter receptors.

L14 ANSWER 32 OF 36 BIOSIS

Membrane transport proteins associated with drug resistance expressed in human melanoma.

Schadendorf D, Makki A, Stahr C, van Dyck A, Wanner R, Scheffer GL, Flens MJ, Scheper R, Henz BM.

Department of Dermatology, Virchow Clinics, Humboldt University Berlin, Germany.

Melanoma cells often display a multidrug-resistant phenotype, but the mechanisms involved are largely unknown. We have studied here the recently identified transport-associated proteins, MRP and LRP, and the well-known drug resistance marker P-glycoprotein using a panel of 16 human melanoma cell lines and 71 benign and malignant melanocytic tissue samples. By flow cytometry and immunohistochemistry, expression of P-glycoprotein was not detectable on the protein level in the 10 cell lines analyzed, although by reverse transcriptase polymerase chain reaction, MDR-1 gene expression was demonstrated in 2 of 10 cell lines. In addition, immunohistology revealed P-glycoprotein expression in only 1 of 71 melanocytic lesions. In contrast, MRP was detected in a subset of melanoma cell lines by reverse transcriptase polymerase chain reaction and immunohistology (4 of 10). LRP expression was observed in 8 of 10 melanoma cell lines by immunochemistry and in 10 of 10 by reverse transcriptase polymerase chain reaction. Furthermore, MRP was detected immunohistologically in almost 50% of primary and metastatic melanoma specimens, although no significant differences were found between metastases taken before or after chemotherapy. Expression of LRP was detected in a subset of nevi with nevus cells exhibiting up to 25% positive LRP reactivity. In 13 of 21 primary melanomas and 23 of 37 metastases, more than 25% of tumor cells were stained by the LRP-56 monoclonal antibody. Particularly in the group of metastases with more than 50% of LRP-positive cells, 7 of 11 of the metastases had been previously exposed to chemotherapeutic drugs. Although the expression of membrane transport proteins may explain only the chemoresistance toward lipophilic, natural compounds and not resistance against alkylating agents, the lack of P-glycoprotein expression after chemotherapeutic treatment and the significant expression of MRP and LRP in melanoma cells provide first

insights into the drug-resistant phenotype in melanoma. Additional studies analyzing the role of MRP and LRP in chemoresistance of melanoma are warranted.

PMID: 7495278 [PubMed - indexed for MEDLINE]

1: Br J Dermatol 2001 Apr;144(4):745-50 Related Articles, NEW Books, LinkOut

online

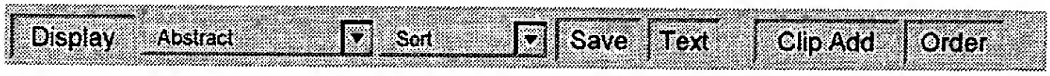
Chemotherapy induces or increases expression of multidrug resistance-associated protein in malignant melanoma cells.

Ichihashi N, Kitajima Y.

Department of Dermatology, Gifu University School of Medicine, 40 Tukasa-machi, Gifu City 500-8705, Japan. ichihasi@cc.gifu-u.ac.jp

BACKGROUND: Human malignant melanoma is notoriously resistant to chemotherapeutic agents. Melanoma-derived cell lines are often markedly chemoresistant, suggesting that cellular mechanisms mediate generation of the multidrug resistance (MDR) phenotype. This phenotype is often due to P-glycoprotein (Pgp) and the MDR-associated protein (MRP), which are drug transporter proteins associated with resistance to a broad spectrum of lipophilic drugs. OBJECTIVES: To determine the relationships between the expression of the MDR gene MDR-1 (the product of which is Pgp) or the MRP gene, and clinical chemoresistance of malignant melanoma. METHODS: We examined changes in the expression of MDR-1 and MRP genes at the mRNA level before and after chemotherapy by reverse transcription-polymerase chain reaction (RT-PCR) analysis using formalin-fixed, paraffin-embedded sections of 18 specimens taken from eight melanoma patients. mRNA expression of the MDR-1 and MRP gene-specific PCR products was quantitatively determined by densitometry and compared with that of an internal standard (beta-actin). RESULTS: Five of seven primary melanomas were found to express the MRP gene to a certain extent even before chemotherapy. After first and second courses of chemotherapy, six patients had an increased ratio of MRP mRNA to beta-actin mRNA compared with the prechemotherapy levels in the same patients. None of the cases of melanoma expressed MDR-1. CONCLUSIONS: These results suggest that a significant mRNA level of MRP gene was intrinsically present in malignant melanoma even before exposure to chemotherapeutic drugs and increased in its expression after chemotherapy, suggesting that MRP plays a part in increasing the chemoresistance of malignant melanoma during chemotherapy.

PMID: 11298532 [PubMed - indexed for MEDLINE]



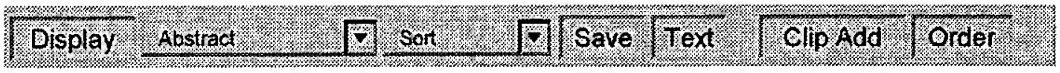
Identification of differentially expressed genes in human melanoma cells with acquired resistance to various antineoplastic drugs.

Grottke C, Mantwill K, Dietel M, Schadendorf D, Lage H.

Institute of Pathology, Charite, Campus Mitte, Humboldt University Berlin, Berlin, Germany.

Malignant melanoma displays strong resistance against various antineoplastic drugs. The mechanisms conferring this intrinsic resistance are unclear. To better understand the molecular events associated with drug resistance in melanoma, a panel of human melanoma cell variants exhibiting low and high levels of resistance to 4 commonly used drugs in melanoma treatment, i.e., vindesine, etoposide, fotemustine and cisplatin, was characterized by differential display reverse transcription-polymerase chain reaction (DDRT-PCR). Of 269 mRNA fragments found to be altered in expression level by DDRT-PCR, a total of 11 cDNA clones was characterized after confirmation of a differential expression pattern by Northern blot analyses. These clones include 3 genes (DSM-1, DSM-3 and DSM-5) of known function, 4 previously sequenced genes (DSM-2, DSM-4, DSM-6 and DSM-7) of uncharacterized function and 4 novel genes (DSM-8-DSM-11) without match in GenBank. All of these genes exhibited altered mRNA expression in high level etoposide-resistant cells, whereby 7 genes (DSM-1-DSM-6 and DSM-8) were found to be decreased in the transcription rate in these etoposide-resistant cells. The mRNA synthesis of the remaining genes (DSM-7 and DSM-9-DSM11) was enhanced in high level etoposide-resistant melanoma cells. The expression of 5 (DSM-5 and DSM-7-DSM-10) of the cloned cDNA encoding mRNAs was modulated in various independently established drug-resistant melanoma cells, indicating to be associated with drug resistance. Further characterization of these genes may yield inside into the biology and development of drug resistance in malignant melanoma.

PMID: 11058868 [PubMed - indexed for MEDLINE]



1: Pharmacotherapy. 1984 Mar-Apr;4(2):61-73. Related Articles, Links

Entrez PubMed

PubMed Services

Related Resources

Etoposide: a semisynthetic epipodophyllotoxin. Chemistry, pharmacology, pharmacokinetics, adverse effects and use as an antineoplastic agent.

Sinkule JA.

Etoposide (VP 16) is a semi-synthetic derivative of 4'-demethylepipodophyllotoxin , a naturally occurring compound synthesized by the North American May apple (Podophyllum peltatum) and the Indian species Podophyllum emodi Wallich . Although podophyllotoxins are classical spindle poisons causing inhibition of mitosis by blocking mitrotubular assembly, etoposide inhibits cell cycle progression at a premitotic phase (late S and G2), probably via inhibition of DNA synthesis. There appears to be a selective antileukemic dose response relationship when compared to normal hematopoietic elements. Etoposide is effective when administered orally at about twice the recommended parenteral dosage. Schedule dependency in both animal models and clinical trials has been observed; multiple dosing over three to five consecutive days is superior to weekly single dose administration. Etoposide's dose-limiting toxicity is myelosuppression (leukopenia), which is quite predictable; alopecia and GI toxicity (nausea, vomiting, stomatitis) occur in about 20-30% of patients given recommended dosages. Etoposide appears to be one of the most active drugs for small cell lung cancer, testicular carcinoma (the Food and Drug Administration approved indication), ANLL and malignant lymphoma. Etoposide also has demonstrated activity in refractory pediatric neoplasms, hepatocellular, esophageal, gastric and prostatic carcinoma, ovarian cancer, chronic and acute leukemias and non-small cell lung cancer, although additional single and combination drug studies are needed to substantiate these data. Its contribution in front-line combination chemotherapeutic regimens for these cancers will be better defined in the forthcoming years. Etoposide appears to have minimal activity in breast cancer and, based on current data, it is inactive against malignant melanoma, colorectal adenocarcinoma and cancer of the head and neck, although the dosage and schedules used in many of the Phase II studies may have been suboptimal.

Publication Types:
- Clinical Trial

- Review

PMID: 6326063 [PubMed - indexed for MEDLINE]

1: Anticancer Res 1999 Sep-Oct;19(5C):4413-20

Multidrug resistant malignant melanoma with intracranial metastasis responding to immunotherapy.

Savas B, Arslan G, Gelen T, Karpuzoglu G, Ozkaynak C.

Department of Internal Medicine, Akdeniz University Medical School, Antalya, Turkey. Savasb@med.akdeniz.edu.tr

Metastatic malignant melanoma (MM) is well known for its poor response to chemotherapy, radiotherapy, and its remarkable susceptibility to interleukin-2 (IL-2) based immunotherapies. MM with brain metastatis in particular, has 4-5 months life expectancy from metastasis to death. Drug efflux pumps such as P-glycoprotein (P-gp), or drug detoxifying mechanisms e.g. glutathion epsilon S-transferase-pi (GST) are some of the possible multidrug resistance (MDR) mechanisms in MM. Here we report the first P-gp+ MDR MM with brain metastasis in the literature, demonstrating a remarkable response to IL-2, interferon-alpha (IFN), 5-fluorouracil (5FU) regimen. A 41-year old man was admitted with multiple inoperable brain lesions. Biopsies from intracranial and dermal lesions revealed MM. Cisplatin, carmustine, dacarbazine, tamoxifen (CCDT) together with external cranial radiotherapy were administered, and partial response in lesions and symptoms was achieved. However, after the third course of CCDT treatment, he was admitted to the emergency ward with dramatically increased intracranial lesions, and recurring dermal lesions. A biopsy from the recurred lesions revealed that MM cells were P-gp+, but GST. Administration of a IL-2, IFN and 5FU regimen achieved a remarkable decline in the brain lesions with almost total disappearance of symptoms. He was well and capable of doing work for 18 months. Dermal lesions had not recurred since the beginning of immunotherapy. In contrast, another 34-year old man who developed brain metastases after CCDT for MM, was negative for P-gp and GST. Cranial radiotherapy was started and the above mentioned IL-2 based regimen was administered. However, no response was observed. These two cases together with previous studies demonstrating the susceptibility of P-gp+ MDR cancer cell lines to IL-2 activated killer (LAK) cells in this report suggest that P-gp+ MDR MM is probably a good candidate for IL-2 based treatments.

PMID: 10650785 [PubMed - indexed for MEDLINE]

L10 ANSWER 1 OF 1 USPATFULL

ACCESSION NUMBER:	2002:181520 USPATFULL
TITLE:	DR6 and uses thereof
INVENTOR(S):	Jin, Shengfang, West Roxbury, MA, United States Shyjan, Andrew W., Nahant, MA, United States Van Huffel, Christophe, Cambridge, MA, United States
PATENT ASSIGNEE(S):	Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6423494	B1	20020723
APPLICATION INFO.:	US 1999-470175		19991222 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-276401, filed on 25 Mar 1999		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Huff, Sheela		
ASSISTANT EXAMINER:	Harris, Alana M.		
LEGAL REPRESENTATIVE:	Fish & Richardson, P. C.		
NUMBER OF CLAIMS:	15		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 1 Drawing Page(s)		
LINE COUNT:	3164		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . for treating a drug resistant tumor in a patient, the method comprising administering to said subject an amount of a **MDA-9** antagonist effective to reduce **drug resistance** of said tumor in the patient. In another aspect, the invention features the use of an inhibitor of MDA-9 expression,. . .

Anthracyclines
2 Daunorubicin

WO 98/46736

most all Differ 3

1996 4, 317-333

L7 ANSWER 26 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1996:392529 BIOSIS

DOCUMENT NUMBER: PREV199699114885

TITLE: Circulating clonal cells in multiple myeloma have the phenotype of bone marrow plasma cells.

AUTHOR(S): Rawstron, A. C.; Owen, R. G.; Child, J. A.; Morgan, G. J.; Jack, A. S.

CORPORATE SOURCE: Haematol. Malignancy Diagnostic Serv., General Infirmary, Leeds UK

SOURCE: British Journal of Haematology, (1996) Vol. 93, No. SUPPL. 2, pp. 126.
Meeting Info.: Second Meeting of the European Haematology Association Paris, France May 29-June 1, 1996
ISSN: 0007-1048.

DOCUMENT TYPE: Conference

LANGUAGE: English

L9 ANSWER 8 OF 22 MEDLINE
ACCESSION NUMBER: 96103407 MEDLINE
DOCUMENT NUMBER: 96103407
TITLE: Alterations of melanin synthesis in human melanoma cells selected in vitro for multidrug resistance.
AUTHOR: Stromskaya T P; Filippova N A; Rybalkina EYu; Egudina S V; Shtil A A; Eliseenkova A V; Stavrovskaya A A
CORPORATE SOURCE: Laboratory of Tumor Cell Genetics, Cancer Research Center of Russian Academy of Medical Sciences, Moscow.
SOURCE: EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY, **(1995 May)** 47 (2-3) 157-66.
Journal code: BIR. ISSN: 0940-2993.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602

AB Previous data showing the correlation of multidrug resistance (MDR) and **differentiation** in tumor cell populations (Melloni et al. 1988; Stavrovskaya et al. 1990) suggest that: 1) isolation of MDR cells by cytostatic drugs leads to the selection of more **differentiated** cell variants and 2) in more **differentiated** cell variants the activity of MDR-related P-glycoprotein (Pgp) is more prominent than in less **differentiated** cells. Here we used human **melanoma** cell line mS and two variants selected from mS population: a) MDR variant of mS selected by colchicine (mS-0.5) and b) mS-trRAR/2--variant obtained by introduction of expressing retinoic acid receptor RAR-alpha cDNA into mS cell. The **differentiation** status, expression of MDR1 **gene** and Pgp functioning were compared in wild-type cells and mS variants. Electron microscopic examination of melanosomes showed that the mS-0.5 subline comprised more **differentiating** cells in the population than parental mS cultures and that these cells were at later stages of melanogenesis. The increase in the degree of **differentiation** in mS-0.5 population coincided with MDR1 **gene** overexpression, occurrence of Pgp molecules on the cell membrane and acceleration of Pgp-mediated Rhodamine 123 (Rh123) efflux. mS-trRAR/2, proved to be more **differentiated** than mS cells. The MDR1 mRNA level and Rh123 efflux were not elevated in mS-trRAR/2 cells, however, retinoic acid (RA) treatment increased both the degree of **differentiation** and Rh123 efflux in mS-trRAR/2 to a greater extent than in mS cultures. Thus, the data obtained in this study are in favor of the suppositions mentioned above. The mechanisms of coordinated alterations of **differentiation** and Pgp activity in MDR cells are discussed.

L9 ANSWER 2 OF 22 MEDLINE
ACCESSION NUMBER: 1998297844 MEDLINE
DOCUMENT NUMBER: 98297844
TITLE: Elevated expression of S100P, CAPL and MAGE 3 in doxorubicin-resistant cell lines: comparison of mRNA differential display reverse transcription-polymerase chain reaction and subtractive suppressive hybridization for the analysis of differential gene expression.
AUTHOR: Bertram J; Palfner K; Hiddemann W; Kneba M
CORPORATE SOURCE: Department of Hematology/Oncology, University of Gottingen, Germany.
SOURCE: ANTI-CANCER DRUGS, **(1998 Apr)** 9 (4) 311-7.
Journal code: A9F. ISSN: 0959-4973.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY WEEK: 19981004

AB Subtractive suppressive hybridization (SSH) and mRNA **differential** display reverse transcription-polymerase chain reaction (DDRT-PCR) were compared for their ability to detect the expression of **drug-resistance** associated **genes** in a doxorubicin-resistant and -sensitive colon carcinoma cell line (LoVo H67P). The expression pattern of more than 9000 bands obtained by DDRT-PCR were identical in both cell lines by more than 95%. Of the remaining **differentially** expressed DDRT-PCR products, 21 cDNA fragments were further analyzed after cloning. A total of 210 clones were sequenced resulting in 40 **different** sequences of which only five were **differentially** expressed as revealed by Northern blot analysis. SSH, on the other hand, resulted in 30 **different** sequences of 37 clones analyzed. Thirteen of 30 sequences (43%) could be identified by databank analysis (excluding expressed sequence tags) in contrast to nine of 40 clones (23%) obtained by DDRT-PCR. Of the clones identified by SSH, 60% exhibited a **differential** expression comparing the doxorubicin-resistant and -sensitive cell line, respectively, as compared to only 13% of the DDRT-PCR derived clones. The application of SSH resulted in the identification of **differentially** expressed **genes** in three doxorubin-resistant cell lines (LoVo DxR, ARH D60 and KB-V1) as compared to the sensitive parental cell lines. A significant higher expression of S100P, a protein involved in calcium metabolism, as well as MAGE 3 (**melanoma antigen gene**) was found in the resistant cell lines using this methodology. The expression of CAPL, a second protein involved in calcium metabolism, was only moderately elevated in the doxorubicin-resistant cells. We found that subtractive suppressive hybridization proved to be a more rapid and reliable method for the detection of **differentially** expressed mRNAs in our system.

L9 ANSWER 4 OF 22 MEDLINE

ACCESSION NUMBER: 1998155638 MEDLINE
DOCUMENT NUMBER: 98155638
TITLE: Human melanoma cell lines selected in vitro displaying various levels of **drug resistance** against cisplatin, fotemustine, vindesine or etoposide: modulation of proto-oncogene expression.
AUTHOR: Kern M A; Helmbach H; Artuc M; Karmann D; Jurgovsky K; Schadendorf D
CORPORATE SOURCE: Klinische Kooperationseinheit fur Dermato-Onkologie des DKFZ am Klinikum der medizinischen Fakultat Mannheim, Universitat Heidelberg, Germany.
SOURCE: ANTICANCER RESEARCH, **(1997 Nov-Dec)** 17 (6D) 4359-70.
Journal code: 59L. ISSN: 0250-7005.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199805
ENTRY WEEK: 19980504

AB **Melanoma** cells often display a multidrug-resistant phenotype, but the mechanisms involved are largely unknown. In order to establish a reproducable model system for studying the exact mechanisms conferring chemoresistance, we selected **drug-resistant** sublines in vitro derived from one parental human **melanoma** (MeWo) cell line. Four commonly used chemotherapeutic drugs (vindesine, etoposide, fotemustine, cisplatin) with **different** modes of action were choosen and stable sublines exhibiting four **different** levels of resistance against each drug were selected by continuous exposure over two years. Analysis of the **drug-resistant** sublines regarding their pharmacological characteristics and cross-resistance pattern revealed an up to 26-fold increased relative resistance against the alkylating agent fotemustine (MeWoFOTE) and an up to 35.7-fold increased relative resistance against topoisomerase-II-inhibiting etoposide (MeWoETO). Cisplatin selection (MeWoCIS) resulted in a 6-fold higher resistance compared to parental MeWo cells, whereas vindesine exposure (MeWoVIND) increased relative resistance up to 10.2-fold. Sublines selected separately for resistance to the DNA-damaging agents fotemustine, cisplatin and etoposide demonstrated strong cross-resistance.

In comparison to the parental cell line **drug-resistant** sublines showed altered expression patterns of proto-oncogenes. Levels of p53 mRNA decreased with increasing resistance to vindesine, etoposide and fotemustine. Expression of bcl-2 family members (bax, bcl-x) was modulated by fotemustine, etoposide and cisplatin. In addition the expression of members of the fos (c-fos) and jun (c-jun, jun-D) **gene** family encoding transcription factors of the AP-1 complex was altered in all **drug-resistant** sublines. The pattern of expression varied with the inducing stimulus and this was paralleled by changes in the transactivation potential of AP-1. Our results reinforce the central role of AP-1 in **drug resistance** probably through its participation in a programmed cellular stress response.

L21 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:344859 CAPLUS
DOCUMENT NUMBER: 131:698
TITLE: Modulation of **drug resistance** via ubiquitin carboxy-terminal hydrolase
INVENTOR(S): **Shyjan, Andrew W.**; Macbeth, Kyle J.
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925373	A1	19990527	WO 1998-US24324	19981113
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5932422	A	19990803	US 1997-970733	19971114
AU 9914091	A1	19990607	AU 1999-14091	19981113
US 6322982	B1	20011127	US 1999-365405	19990802
PRIORITY APPLN. INFO.:			US 1997-970733 A	19971114
			WO 1998-US24324 W	19981113

AB The expression of ubiquitin carboxy-terminal hydrolase is aberrant in cells that are resistant to treatment with chem. agents. Accordingly, the invention features methods for diagnosing and treating drug-resistant cells (e.g., tumor cells) by examg. and modulating the expression or activity of UCH.

L3 ANSWER 4 OF 8 MEDLINE
ACCESSION NUMBER: 1998054294 MEDLINE
DOCUMENT NUMBER: 98054294 PubMed ID: 9391086
TITLE: **Syntenin**, a PDZ protein that binds syndecan cytoplasmic domains.
AUTHOR: Grootjans J J; Zimmermann P; Reekmans G; Smets A; Degeest G; Durr J; David G
CORPORATE SOURCE: Laboratory for Glycobiology and Developmental Genetics, Center for Human Genetics, University of Leuven, and Flanders Interuniversity Institute for Biotechnology, 3000 Leuven, Belgium.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 Dec 9)** 94 (25) 13683-8.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF000652
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980115

AB The syndecans are transmembrane proteoglycans that place structurally heterogeneous heparan sulfate chains at the cell surface and a highly conserved polypeptide in the cytoplasm. Their versatile heparan sulfate moieties support various processes of molecular recognition, signaling, and trafficking. Here we report the identification of a protein that binds to the cytoplasmic domains of the syndecans in yeast two-hybrid screens, surface plasmon resonance experiments, and ligand-overlay assays. This protein, **syntenin**, contains a tandem repeat of PDZ domains that reacts with the FYA C-terminal amino acid sequence of the syndecans. Recombinant enhanced green fluorescent protein (eGFP)-**syntenin** fusion proteins decorate the plasmamembrane and intracellular vesicles, where they colocalize and cosegregate with syndecans. Cells that overexpress eGFP-**syntenin** show numerous cell surface extensions, suggesting effects of **syntenin** on cytoskeleton-membrane organization. We propose that **syntenin** may function as an adaptor that couples syndecans to cytoskeletal proteins or cytosolic downstream signal-effectors.

L3 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L9 ANSWER 2 OF 3 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998172741 MEDLINE
DOCUMENT NUMBER: 98172741 PubMed ID: 9511750
TITLE: Melanoma differentiation associated gene-9, **mda-9**, is a human gamma interferon responsive gene.
AUTHOR: Lin J J; Jiang H; Fisher P B
CORPORATE SOURCE: Department of Pathology, Herbert Irving Comprehensive Cancer Center, Columbia University, College of Physicians and Surgeons, New York, NY 10032, USA.
SOURCE: GENE, (1998 Jan 30) 207 (2) 105-10.
Journal code: FOP; 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF006636 AF006652
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980410
Last Updated on STN: 19980410
Entered Medline: 19980330

AB Subtraction hybridization using a cDNA library prepared from temporally spaced mRNAs from human melanoma cells treated with recombinant human fibroblast interferon (IFN-beta) plus mezerein (MEZ) that induces terminal differentiation (tester cDNA library) and a temporally spaced cDNA library prepared from actively proliferating melanoma cells (driver cDNA library) produced a Temporally Spaced Subtracted (TSS) cDNA library. This approach resulted in the identification of melanoma differentiation associated (mda) genes displaying both enhanced and suppressed expression during growth inhibition and differentiation. In the present report, we describe a novel cDNA **mda-9** that consists of 2084 nucleotides, and encodes a protein of 298 amino acids with a predicted M(r) of approx. 33 kDa. Treatment of human SV40-immortalized normal melanoma cells with immune interferon, INF-gamma, induces growth suppression and enhances **mda-9** expression without inducing terminal differentiation. These results establish that induction of terminal differentiation in human melanoma cells, using the combination of a type I interferon (IFN-beta) + MEZ, can elicit signaling pathways and gene expression changes also regulated by type II immune interferon.

L58 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999424854 MEDLINE
DOCUMENT NUMBER: 99424854 PubMed ID: 10496535
TITLE: PDZK1, a novel **PDZ** domain-containing protein up-regulated in carcinomas and mapped to chromosome 1q21, interacts with cMOAT (MRP2), the **multidrug resistance**-associated protein.
AUTHOR: Kocher O; Comella N; Gilchrist A; Pal R; Tognazzi K; Brown L F; Knoll J H
CORPORATE SOURCE: Department of Pathology, Beth Israel-Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215, USA.. okocher@caregroup.harvard.edu
SOURCE: LABORATORY INVESTIGATION, **(1999 Sep)** 79 (9) 1161-70.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991007

AB We recently reported the isolation and partial characterization of two novel proteins, MAP17 and PDZK1. Using in situ hybridization, we demonstrated that MAP17 and PDZK1 mRNAs are markedly up-regulated in human carcinomas. PDZK1, originally isolated as a protein interacting with MAP17, contains four PDZ protein-interaction domains and could potentially interact with as many as four target proteins. In this paper, we confirm the overexpression of PDZK1 in human carcinomas using a specific antibody and demonstrate the localization of the PDZK1 gene to human chromosome 1q21, a region frequently altered in neoplastic conditions. Using the yeast two-hybrid system, we have also determined that PDZK1 interacts with the carboxy-terminal portion of cMOAT (MRP2), the canalicular multispecific organic anion transporter associated with multidrug resistance. This is of particular interest because proteins containing PDZ domains are involved in the clustering and signaling pathways of membrane-associated proteins, including ion channels. Therefore, the protein cluster formed by the association of cMOAT, PDZK1, and MAP17 could play an important role in the cellular mechanisms associated with multidrug resistance, and PDZK1 may represent a new target in cancer cells resistant to chemotherapeutic agents.

REMARK INTERACTION WITH EPHB1 AND EPHA7.
REFERENCE 5 (residues 1 to 298)
AUTHORS Fernandez-Larrea,J., Merlos-Suarez,A., Urena,J.M., Baselga,J. and Arribas,J.
TITLE A role for a PDZ protein in the early secretory pathway for the targeting of proTGF-alpha to the cell surface
JOURNAL Mol. Cell 3 (4), 423-433 (1999)
MEDLINE 99247010
PUBMED 10230395
REMARK FUNCTION, AND INTERACTION WITH TGFA.
REFERENCE 6 (residues 1 to 298)
AUTHORS Grootjans,J.J., Reekmans,G., Ceulemans,H. and David,G.
TITLE Syntenin-syndecan binding requires syndecan-synteny and the co-operation of both PDZ domains of syntenin
JOURNAL J. Biol. Chem. 275 (26), 19933-19941 (2000)
MEDLINE 20347906
PUBMED 10770943
REMARK INTERACTION WITH SYNDECANS; NRXN2 AND EPHB1.
REFERENCE 7 (residues 1 to 298)
AUTHORS Jannatipour,M., Dion,P., Khan,S., Jindal,H., Fan,X., Laganiere,J., Chishti,A.H. and Rouleau,G.A.
TITLE Schwannomin isoform-1 interacts with syntenin via PDZ domains
JOURNAL J. Biol. Chem. 276 (35), 33093-33100 (2001)
MEDLINE 21413906
PUBMED 11432873
REMARK INTERACTION WITH NF2.
REFERENCE 8 (residues 1 to 298)
AUTHORS Zimmermann,P., Tomatis,D., Rosas,M., Grootjans,J.J., Leenaerts,I., Degeest,G., Reekmans,G., Coomans,C. and David,G.
TITLE Characterization of syntenin, a syndecan-binding PDZ protein, as a component of cell adhesion sites and microfilaments
JOURNAL Mol. Biol. Cell 13, 339-350 (2001)
REMARK FUNCTION, AND SUBCELLULAR LOCATION.
REFERENCE 9 (residues 1 to 298)
AUTHORS Geijsen,N., Uings,I.J., Pals,C., Armstrong,J., McKinnon,M., Raaijmakers,J.A., Lammers,J.W., Koenderman,L. and Coffer,P.J.
TITLE Cytokine-specific transcriptional regulation through an IL-5Ralpha interacting protein
JOURNAL Science 293 (5532), 1136-1138 (2001)
MEDLINE 21390055
PUBMED 11498591
REMARK FUNCTION, AND INTERACTION WITH IL5RA.
COMMENT ----------

----------.

[FUNCTION] Seems to function as an adapter protein. In adherens junctions may function to couple syndecans to cytoskeletal proteins or signaling components. Seems to couple transcription factor SOX4 to the IL-5 receptor (IL5RA). May also play a role in vesicular trafficking. Seems to be required for the targeting of TGFA to the cell surface in the early secretory pathway.
[SUBUNIT] Monomer and homodimer (By similarity). Interacts with SDC1, SDC2, SDC3, SDC4, NRXN2, EPHA7, EPHB1, NF2 isoform 1, TGFA and IL5RA. Interacts with neurofascin, SDCBP2 and PTPRJ (By similarity).
[SUBCELLULAR LOCATION] Mainly membrane-associated. Localized to adherens junctions, focal adhesions and endoplasmic reticulum. Colocalized with actin stress fibers. Also found in the nucleus.
[TISSUE SPECIFICITY] Widely expressed. Expressed in fetal kidney, liver, lung and brain. In adult highest expression in heart and placenta.

```
            [INDUCTION] By gamma interferon in melanoma cells.
            [PTM] Phosphorylated on tyrosine residues.
            [SIMILARITY] CONTAINS 2 PDZ/DHR DOMAINS.
FEATURES             Location/Qualifiers
     source          1..298
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
     gene            1..298
                     /gene="SDCBP"
                     /note="synonyms: MDA9, SYCL"
     Protein         1..298
                     /gene="SDCBP"
                     /product="Syntenin 1"
     Region          62
                     /gene="SDCBP"
                     /region_name="Conflict"
                     /note="N -> S (IN REF. 2)."
     Region          69
                     /gene="SDCBP"
                     /region_name="Variant"
                     /note="N -> S (IN DBSNP:1127509). /FTId=VAR_013160."
     Region          114..193
                     /gene="SDCBP"
                     /region_name="Domain"
                     /note="PDZ 1."
     Region          198..273
                     /gene="SDCBP"
                     /region_name="Domain"
                     /note="PDZ 2."
ORIGIN
        1 mslypsledl kvdkviqaqt afsanpanpa ilseasapip hdgnlyprly pelsqymgls
       61 lneeeiranv avvsgaplqg qlvarpssin ymvapvtgnd vgirraeikq girevilckd
      121 qdgkiglrlk sidngifvql vqanspaslv glrfgdqvlq ingencagws sdkahkvlkq
      181 afgekitmti rdrpfertit mhkdstghvg fifkngkits ivkdssaarn glltehnice
      241 ingqnviglk dsqiadilst sgtvvtitim pafifehiik rmapsimksl mdhtipev
//
```

L9 ANSWER 1 OF 22 MEDLINE
ACCESSION NUMBER: 1998330212 MEDLINE
DOCUMENT NUMBER: 98330212
TITLE: Influence of exogenous RAR alpha gene on MDR1 expression and P-glycoprotein function in human and rodent cell lines.
AUTHOR: Stromskaya T P; Rybalkina E Y; Shtil A A; Zabotina T N; Filippova N A; Stavrovskaya A A
CORPORATE SOURCE: Cancer Research Center of Russian Academy of Medical Sciences, Moscow.
SOURCE: BRITISH JOURNAL OF CANCER, **(1998 Jun)** 77 (11) 1718-25.
Journal code: AV4. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199810
ENTRY WEEK: 19981001

AB The goal of our study was to obtain direct evidence of co-ordinated regulation of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) and **differentiation** in tumour cells and to study some signalling pathways involved in joint regulation of these two cell phenotypes. The sublines of human **melanoma** (mS) and hepatoma (human HepG2 and rat McA RH 7777) cell lines were obtained by retroviral infection of the wild-type cells with the cDNA of the human retinoic acid receptor alpha (RAR alpha). The resulting sublines stably overexpressed exogenous RAR alpha **gene**. The infectants became more **differentiated** than the parental cells as determined by a decrease in the synthesis of the embryo-specific alpha-fetoprotein in HepG2 and McA RH 7777 hepatoma cells and by an increase in melanin synthesis in mS cells. The **differentiation** of human cells was accompanied by an increase in the amounts of MDR1 mRNA but not by an increase in P-gp activity as a drug transporter, in contrast, in the rat RAR alpha overexpressing cells P-gp functional activity was elevated. Treatment with cytotoxic drug (colchicine) or retinoic acid (RA) resulted in a slight increase in P-gp activity in the parental and RAR alpha-infected **melanoma** cells, whereas the increase in P-gp function in the infected hepatoma cells (both human and rat) was very prominent. Thus, we provide new evidence that cell **differentiation** caused by the overexpression of the **gene** participating in the **differentiation** programme leads to overexpression of MDR1 **gene** and **drug resistance** and that this effect is tissue and species specific. These data imply that the activation of the RA-controlled signalling pathway up-regulates MDR1 **gene** expression.

L50 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:962222 CAPLUS
DOCUMENT NUMBER: 124:75751
TITLE: Circumvention of P-glycoprotein-mediated multiple drug resistance by phosphorylation modulators is independent of protein kinases
AUTHOR(S): Smith, Charles D.; Zilfou, Jack T.
CORPORATE SOURCE: Dep. Pharmacol., Fox Chase Cancer Cent., Philadelphia, PA, 19111, USA
SOURCE: Journal of Biological Chemistry (1995), 270(47), 28145-52
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expression of P-glycoprotein by tumor cells confers resistance to multiple natural product drugs because of its ability to export these compds. This transporter is a substrate for several protein kinases; however, the functional significance of its phosphorylation is not defined. We examd. the effects of many activators and inhibitors of protein kinases on the activity of P-glycoprotein in drug-resistant human breast carcinoma cells (MCF-7/ADR). Several phorbol esters sensitized these cells to P-glycoprotein substrate drugs; however, there was no correlation with activation of protein kinase C. The 4.alpha.- and 4.beta.-isomers of phorbol 12-myristate 13-acetate were equally potent in sensitizing the cells to actinomycin D and daunomycin and in increasing the intracellular accumulation of [3H]vinblastine. These effects of 4.beta.-phorbol myristate acetate required much higher concns. than were needed to increase P-glycoprotein phosphorylation and were not antagonized by staurosporine. Similar to verapamil, the phorbol esters did not sensitize MCF-7/ADR cells to cisplatin, nor parental MCF-7 cells to any of the anticancer drugs. Mezerein, K-252a, and H-89 sensitized MCF-7/ADR cells, increased intracellular accumulation of [3H]vinblastine, and antagonized photolabeling of P-glycoprotein by [3H]azidopine. Therefore, phosphorylation does not appear to play a significant role in regulating P-glycoprotein activity in MCF-7/ADR cells.

WEST

End of Result Set

☐ Generate Collection Print

L31: Entry 32 of 32 File: USPT Dec 23, 1980

DOCUMENT-IDENTIFIER: US 4241187 A
TITLE: Method and apparatus for cell and tissue culture

Application Filing Date (1):
19790327

Brief Summary Text (3):
Biological cells and tissues cultured in vitro are commonly employed in various biomedical applications, such as, for example, in the development and production of various vaccines, and for the in vitro screening of potential anti-cancer agents prior to in vivo testing in laboratory test animals. The culture systems presently in use typically employ synthetic culture media as the source for the cell nutrients, and for the most part, are incapable of supporting high density cell growth. With such systems, it has been found to be extremely difficult to obtain substantial quantities of cultured cells and tissues which maintain their in vivo function.

L7 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:498185 CAPLUS
DOCUMENT NUMBER: 103:98185
TITLE: Experimental chemotherapy of melanoma
AUTHOR(S): Gupta, Vicram
CORPORATE SOURCE: Dep. Intern. Med., Univ. Texas, Galveston, TX, 77550, USA
SOURCE: Clin. Manage. Malig. Melanoma (1984), 151-65.
Editor(s): Costanzi, John J. Mijhoff: Boston, Mass.
CODEN: 54BPA7
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with 115 refs., discussing 2 exptl. approaches (one investigating std. or new **anticancer agents** utilizing **animal models** or tissue culture cell lines and the other by manipulating the melanin biosynthetic pathway for potentially selective drug toxicity to melanoma cells) in relation to studies of **drug sensitivity** in vitro or in vivo and modulation of melanoma growth.

PMID: 1283846 [PubMed - indexed for MEDLINE]

Other Reference Publication (43):
Sumizawa, T. et al. (1994) "Non-P-Glycoprotein-Mediated Multidrug-Resistant Human KB Cells Selected in Medium Containing Adriamycin,
Cepharanthine, and Mezerein" Somatic Cell and Molecular Genetics 20(5): 423-435.

L14 ANSWER 3 OF 36 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999424854 MEDLINE
DOCUMENT NUMBER: 99424854 PubMed ID: 10496535
TITLE: PDZK1, a novel **PDZ** domain-containing protein up-regulated in carcinomas and mapped to chromosome 1q21, interacts with cMOAT (MRP2), the **multidrug resistance**-associated protein.
AUTHOR: Kocher O; Comella N; Gilchrist A; Pal R; Tognazzi K; Brown L F; Knoll J H
CORPORATE SOURCE: Department of Pathology, Beth Israel-Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215, USA.. okocher@caregroup.harvard.edu
SOURCE: LABORATORY INVESTIGATION, **(1999 Sep)** 79 (9) 1161-70.
Journal code: KZ4; 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991007

AB We recently reported the isolation and partial characterization of two novel proteins, MAP17 and PDZK1. Using in situ hybridization, we demonstrated that MAP17 and PDZK1 mRNAs are markedly up-regulated in human carcinomas. PDZK1, originally isolated as a protein interacting with MAP17, contains four **PDZ** protein-interaction domains and could potentially interact with as many as four target proteins. In this paper, we confirm the overexpression of PDZK1 in human carcinomas using a specific antibody and demonstrate the localization of the PDZK1 gene to human chromosome 1q21, a region frequently altered in neoplastic conditions. Using the yeast two-hybrid system, we have also determined that PDZK1 interacts with the carboxy-terminal portion of cMOAT (MRP2), the canalicular multispecific organic anion **transporter** associated with **multidrug resistance**. This is of particular interest because proteins containing **PDZ** domains are involved in the clustering and signaling pathways of membrane-associated proteins, including ion channels. Therefore, the protein cluster formed by the association of cMOAT, PDZK1, and MAP17 could play an important role in the cellular mechanisms associated with **multidrug resistance**, and PDZK1 may represent a new target in cancer cells resistant to chemotherapeutic agents.

L21 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:712338 CAPLUS
DOCUMENT NUMBER: 129:311732
TITLE: Cloning and cDNA sequence of a human **multidrug resistance**-associated polypeptide and its use in improving the effectiveness of cancer chemotherapy
INVENTOR(S): **Shyjan, Andrew**
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9846736	A1	19981022	WO 1998-US7673	19980416
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6162616	A	20001219	US 1997-843459	19970416
US 5994130	A	19991130	US 1997-1273	19971231
AU 9871254	A1	19981111	AU 1998-71254	19980416

PRIORITY APPLN. INFO.: US 1997-843459 A 19970416
WO 1998-US7673 W 19980416

AB Compns. and methods are disclosed for improving the effectiveness of a chemotherapeutic regimen to eradicate **multidrug-resistant** transformed cells from the body of a mammal, preferably from the body of a human. The present disclosure capitalizes on the discovery of a novel **multidrug-resistance** assocd. protein (MRP), herein designated MRP-.beta.. A unique fragment of the novel MRP-.beta. gene was identified by computer-assisted screening of a nucleic acid database corresponding to a human endothelial cell expression library; this probe was used for hybridization screening of the HUMVEC expression library for the presence of MRP-.beta. cDNAs. The disclosed compns. include MRP-.beta. nucleic acids, including probes and antisense oligonucleotides, MRP-.beta. polypeptides and antibodies, MRP-.beta. expressing host cells, and non-human mammals transgenic or nullizygous for MRP-.beta.. The disclosed methods include methods for attenuating aberrant MRP-.beta. gene expression, protein prodn. and/or protein function. In addn., methods are disclosed for identifying and using a modulator, such as an inhibitor, of MRP-.beta.. Preferably, the modulator is a small mol.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS